Anticholinergics and Central Nervous System Effects: Are We Confused?

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The central nervous system (CNS) effects of anticholinergic agents have been documented in various patient populations and to varying degrees in case reports, brain-activity surrogates, and computerized cognitive testing. The older patient population with overactive bladder represents a group at increased risk of cognitive impairment and other CNS side effects associated with antimuscarinic agents. The complexity of the effect of anticholinergic agents on CNS function requires an increased level of careful investigation. Studies need to be performed in the at-risk population with multiple, validated tests at clinically prescribed doses in acute and chronic situations. These studies need to take into account the effect of commonly prescribed dosing regimens, with doses selected to represent with equivalent bladder potency. The alterations in the serum levels and parent/metabolite effects contributed by metabolic issues or drug delivery systems require special attention.
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The current standard of care for older patients with overactive bladder (OAB) is a combination of behavioral and pharmacologic therapy. Anticholinergic agents are the mainstay of drug therapy. These agents exert their activity by blocking the effects of acetylcholine at muscarinic receptors of the bladder, and are therefore referred to as antimuscarinics (AMs). A recognized category of adverse events for the AM drug class is the potential for central nervous system (CNS) effects. Most physicians consider many of the adverse CNS events as "safety events." The use of AMs for treatment of OAB in the elderly has been tempered as a result of these concerns and is a highly relevant topic for discussion.

OAB is a particularly common condition in the elderly, affecting at least 25% of people over age 65.[1] Those who are cognitively impaired may be more susceptible to CNS events and to further cognitive decline. In addition, portions of the

geriatric population may be at increased risk because of the use of other pharmacologic agents with AM activity (known as anticholinergic load), alterations in metabolism, drug–drug interactions, or additional medical comorbidities. Even a younger population may manifest CNS events, including cognitive changes, dizziness, somnolence, and sedation.

Of note, positive case reports, abnormalities in surrogate measures of CNS function, and alterations in performance on computerized cognitive studies have been published on the CNS effects of some of these agents. However, phase III placebo-controlled and community-use studies have not reported a population effect for CNS events, in part because they report on the population and not the individual occurrences, employ unsolicited CNS adverse-event reporting, enroll a heterogeneous group of patients with varying susceptibility and risk, and utilize a methodology that is underpowered to detect a difference from placebo for a given adverse event. This review also addresses the controversy surrounding how these agents have been and might best be assessed for CNS effects.

AM Pharmacology

Recent reviews have suggested that AMs may work via efferent blockade, the inhibition of the pathway leading to bladder contraction and voiding,[2] and in addition, the afferent pathways that alter the sensory feedback from the bladder.[3] Five distinct muscarinic receptor subtypes (M1-M5) are known to exist.[4] The detrusor muscle of the bladder contains predominantly M2 and M3 receptors, with the M2 subtype approximating 80% of receptors.[5] The M2 receptors have been associated with activity relating to the accommodation of urine during urinary storage, and the minority population of M3 receptors are presumed to be primarily responsible for bladder muscle contraction. However, it has been noted that these functions can be altered in various disease states.[6] AMs have the potential to bind to muscarinic receptors throughout the body in various organ systems and are responsible for the commonly noted adverse events of the drug class; therefore, blockade will not only disrupt activity in the detrusor muscle but will also interfere with other organ systems. For instance, M3 muscarinic receptors are also present in smooth muscle of the bowel, salivary glands, and eyes. Blocking these receptors may cause a relative increase in the adverse effects of constipation, dry mouth, and blurred vision. Alternatively, M2 receptor blockade of the heart may cause a relative increase in heart rate.[7]

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All muscarinic receptor subtypes (M1-M5) are present in the brain.[4] The M1 receptor, predominantly located in the neocortex, is the most abundant subtype in the CNS, hippocampus, and neostratum. M2 receptors are also located throughout the brain. The M3 receptor is also present throughout the CNS, but in relatively lower density. M4 receptors are abundant in the neostriatum, and M5 receptors have been localized in the hippocampus and projection neurons of substantia nigra, pars compacta, and ventral tegmental nuclei. It should be noted that the absolute presence of receptors and the binding to receptors does not determine potency or pharmacologic effect. Clinical studies suggest that cognitive impairment, in particular memory loss, may result from antagonism of M1 and, to some extent, M2 or M4 receptors in the CNS.[8,9] Clinically, older patients with existing cognitive impairment and those with early stage dementia, age-associated memory impairment, or mild cognitive impairment can be especially vulnerable to these cognitive side effects.

Central Nervous System Side Effects: The Blood–Brain Barrier

The CNS side effects caused by AMs may vary depending on the ability of the drugs to penetrate the blood–brain barrier (BBB) and the pharmacologic activity on CNS receptors. Penetration of the BBB depends on passive and active transport. The endothelial cells of brain capillaries are sealed by zonulae occludentes and tight junctions and surrounded by astroglial processes, in addition to a collagen matrix and pericytes. Consequently, the electrical resistance across the endothelium is high, and the passage of solutes through the paracellular pathway is greatly restricted. Only small (400-600 Da), unpolarized, lipid-soluble molecules can readily diffuse to pass from capillary blood to brain tissue.

AMs may penetrate the BBB resulting in CNS side effects. The factors determining the penetration of any pharmacologically active parent compound or metabolite include 1) serum concentration (passive diffusion), 2) active transport ("in" or "out"), 3) lipophilicity (predisposition to dissolve in fat vs water), 4) the electrical charge (polarity), and 5) molecular size and configuration (bulk, not purely molecular weight) may influence the extent to which substances penetrate the CNS under normal conditions. Again, it is important to also consider the metabolites of the parent

compounds because these agents may be metabolized to more or less active or inactive compounds, larger or smaller molecules not only in weight (Da) but in size (configuration), and more or less polar agents with subsequent changes in lipophilicity and more prone to transport.

Certainly, small, lipophilic, noncharged molecular compounds (tertiary ammonium groups) pass the BBB more readily than those containing a quaternary ammonium group.[10] With regard to the current OAB medications, the relative ranking of lipophilicity and potential for crossing the BBB is as follows[11]: Of the tertiary amines, darifenacin is more likely to cross than oxybutynin and solifenacin, and these drugs are more likely to pass than tolterodine. Trospium chloride is the lone quaternary amine responsible for increased polarity and decreased permeability in the group. An interesting example of the effects of drug delivery on the potential of a drug to cause an adverse event would be the transdermal delivery of oxybutynin. Transdermal delivery provides a more stable serum level and favorably alters the parent compound oxybutynin to the metabolite N-desethyloxybutynin (DEO) levels (Figure 1). Transdermal delivery theoretically results in decreased systemic adverse events (and potentially CNS events) by 1) decreasing the total anticholinergic load (less oxybutynin and DEO), 2) providing more stable serum levels (decreasing passive CNS diffusion), and 3) reducing the amount of DEO that may possibly penetrate the CNS more readily.

A number of conditions have been shown to increase the BBB permeability. These include increasing age (> 45 y), the use of certain medications, comorbid diseases, and stress.[14-16] A permeable BBB, due to changes in passive barriers, active transport, or efflux mechanisms, would allow compounds thought less likely to cross under normal conditions to have increased penetration to the CNS. It is important to understand that active transport mechanisms (enzyme systems), passive lipid barriers, and cell junctions can change with age. Thus, all AM agents currently available for OAB treatment, irrespective of their physiochemical properties, should be considered to have the potential to cross the BBB and interact with the muscarinic receptors in the CNS.

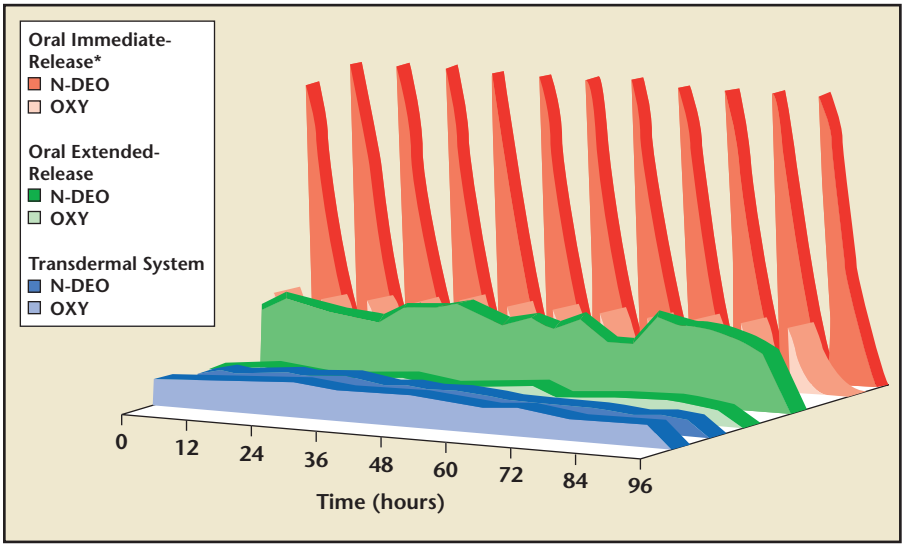

Figure 1. *OXY and N-DEO steady-state plasma concentrations. Transdermal delivery provides a more stable serum level and favorably alters the parent compound oxybutynin to the metabolite N-DEO levels. *Extrapolated concentrations from a single OXY-IR dose of 5 mg/d. N-DEO, N-desethyloxybutynin; OXY, oxybutynin. Data from Guay DR and, New K[12] and Appell RA, et al.[13]*

Cognitive Effects of AMs: Measuring the Clinical Risk

The older OAB patient population represents a group at increased risk of cognitive impairment and other CNS side effects associated with AM agents. There is a documented normal age-related decline in memory function that could result in increased susceptibility to the potential cognitive side effects of AM drugs. Age-related declines in M1 receptor density have been well established. There is a theoretical risk that additional AM antagonism could precipitate an accelerated decline in memory.

The elderly are also likely to be taking other medications that have AM activity, such as antiemetics, tricyclic antidepressants, antihistamines, antispasmodics, and muscle relaxants. The use of these medications adds to the AM burden among older adults and can lead to increased falls among the elderly.[17] Finally, comorbid conditions common in older patients, including cerebrovascular disease, type 2 diabetes mellitus, Parkinson's disease, and Alzheimer's dementia may make these patients more susceptible to cognitive impairment and exaggerate the effects of AM drugs on cognitive function.[18]

Phase III Clinical Data

During phase III placebo-controlled clinical trials and head-to-head clinical trials there has been no statistically significant evidence of increased CNS events greater than the effects of

placebo for any of the AM agents. It should be noted that the method of collection of these CNS adverse events is by unsolicited collection during protocol visits. The studies are also in a heterogeneous population of patients, many of whom are not at high risk, and the small studies are not powered to detect a difference in the incidence of these reports between active agents and placebo. Case studies have demonstrated that oxybutynin can cause cognitive impairment in the elderly population,[19] as well as case reports of what appears to be oxybutynin-related delirium.[20,21] In addition, tolterodine has been associated with CNS case reports.[22] In addition, in the Overactive Bladder: Performance of Extended Release Agents (OPERA)[23] and Overactive Bladder: Judging Effective Control and Treatment (OBJECT)[24] trials, head-to-head studies, no differences were noted among extended-release (ER) oxybutynin twice daily, immediate-release tolterodine, and ER tolterodine with respect to CNS effects recorded or nonelicited CNS adverse events during patient visits.

Chapple and colleagues[25] used pooled data on unsolicited adverse events, including CNS events, from 3 large, multicenter, double-blind, placebo-controlled studies to assess the efficacy, safety, and tolerability of darifenacin. All of the enrolled patients, aged over 18 years, (N = 1049) suffered from OAB for a minimum of 6 months. CNS events were similar to placebo in this population. Staskin and colleagues,[26] utilizing unsolicited adverse events, demonstrated no significant difference from placebo for trospium chloride. Wagg and coauthors[27] reported on a cohort of solifenacin administration specifically in elderly subjects over 65 years of age. They did not report any statistically significant CNS side effects compared with placebo.

Assuming that clinical phase III studies employing an unsolicited CNS adverse events collection are not specific enough to elicit and analyze these events compared with placebo in a study population, the question arises as to the proper methods to document relevant BBB penetration, receptor binding, pharmacologic effect, and subclinical or clinical CNS changes.

Sleep Studies for Potential CNS Effects

The ability of AM agents used for OAB to exert an effect in the CNS has been evaluated in the clinical setting. Using tests such as electroencephalograms (EEG), sleep studies, reaction time tests, and more sophisticated imaging studies, one can measure the effects of specific drug treatments on brain activity, cognitive functioning, or receptor binding.

Utilizing sleep studies, there is evidence that AM compounds influence sleep structure and sleep quality. There are case reports of pavor nocturnus (night terror) after administration of oxybutynin.[28] Two studies compared the effects oxybutynin, tolterodine, and trospium chloride on sleep parameters in healthy subjects. The first study consisted of young (22-36 years), healthy volunteers.[29] The second study was similarly designed and consisted of healthy volunteers over 50 years of age.[30]

Polysomnographic recordings, sleep questionnaires, and psychometric tests (the number combination test and the d2 test of attention[31]) were performed following single doses of oxybutynin, 15 mg; tolterodine, 4 mg; and trospium, 45 mg; or placebo. Rapid eye movement (REM) sleep (relative to total sleep time) was the primary parameter of polysomnography. In young, healthy patients, the REM sleep for oxybutynin was significantly lower than that for trospium chloride and placebo. Of note, the psychometric tests performed during this study did not reveal any differences among the medications. The clinical relevance of these effects is small in healthy young volunteers tested in some of these studies, and the results may not be confidently extended to the at-risk population.

In the second study, consisting of healthy volunteers aged greater than 50 years, there was a reduction of median REM sleep duration after oxybutynin and tolterodine administration, but there was no significant change after trospium administration when compared with placebo. Subjective sleep variables showed no significant change. Sleep duration and quality were not affected by the different medications. Again, none of the study medications influenced the cognitive skills of the volunteers. However, this group of patients had a more distinct impairment of REM sleep after oxybutynin and tolterodine administration than did the younger patients. In both studies, though, the reduction in REM sleep did not reach a pathological degree. Thus, impairment in cognition was not to be expected. The next logical study would be to assess elderly patients who already have impaired sleep or impaired cognition and use these tests to measure the effects of the various AM medications. The elderly patient population has yet to be studied with this technique.

EEG Studies for Potential CNS Side Effects

EEG data have often been reported as a physiological measure of the impact of medications on CNS function. In 1994 Pietzko and coworkers[32] used quantitative evaluation of the multichannel EEG from young, healthy volunteers to study possible CNS adverse effects of oral oxybutynin and oral and intravenous trospium chloride. Oxybutynin was found to cause a distinct and significant power decrease in

various frequency bands of the EEG. Trospium lacked any significant influence on the EEG.

In 2001 Todorova and colleagues[33] investigated the potential CNS adverse effects of 3 AM drugs: oxybutynin, tolterodine, and trospium chloride. Again, the subjects were young, healthy volunteers tested under 3 conditions: at rest with eyes open, at rest with eyes closed, and under mental demand. They found oxybutynin caused significant EEG changes. A clear cumulative effect of the multiple-dose administration was found, with the most pronounced difference from placebo after the second and third doses. In contrast, after administration of tolterodine and placebo the EEG remained essentially within the placebo range.

The EEG effects of darifenacin were studied in healthy volunteers and found to be present but short-lived and not associated with any cognitive changes.[34] Of note, the EEG changes were interpreted by the investigators to be related to brain activity associated with treatment-induced effects on vision, dry mouth, or sensations in the bladder.

Cognitive Studies for Potential CNS Effects

Kay and coworkers[35] randomized 150 healthy patients aged 60 years and older to darifenacin, ER oxybutynin, and placebo. They assessed cognitive function through a battery of computerized tests. In the assessment of delayed recall there was no significant difference between the darifenacin- and placebo-treated groups, but scores for delayed recall were lower in the oxybutynin ER treatment group. Of interest, when screened for self-rated memory the subjects reported no differences between the medications. This discrepancy was interpreted by the authors as an additional risk factor for clinical screening without sophisticated testing; they suggested that the patients were impaired but did not realize it. However, in other quality-of-life studies with OAB patients, statistical changes may be a finding without significant clinical impact. Also, in this study and consistent with the selective M3 activity of the agent, the constipation rate of darifenacin over 3 weeks (7.5 mg, 15 mg) was seen to be 5 times higher (10/49 patients vs 2/50 patients) as an unsolicited adverse event than among the patients taking oxybutynin ER (10 mg, 15 mg, 20 mg).

Lipton and colleagues[36] studied the cognitive effects of darifenacin in volunteers 65 years and older and found it to have no adverse effects. These results were confirmed in a separate study of 400 patients aged over 65 years treated for 12 weeks with darifenacin. Again, no significant CNS side effects were seen during screening for unsolicited adverse events.[37]

A study by Perry and coworkers[38] looked at the postmortem brain morphology of patients confirmed with Parkinson's disease who were over 70 years of age and were receiving treatment with AM agents. They concluded that amyloid plaque densities were more than 2.5-fold higher in patients treated with long-term AM medication when compared with untreated patients or those on short-term treatment. These findings have not been replicated in other studies but have major implications in the use of AMs in the elderly, especially those with Parkinson's disease. Chronic AMs might not be appropriate in older patients.

Conclusions

The complexity of the effect of anticholinergic agents on CNS function requires an increased level of careful investigation. At the molecular level, penetration of the different agents into the CNS with acute and chronic dosing should be determined, as well as the true pharmacologic effect of the agents irrespective of receptor binding but accurately oriented toward CNS potency. Clinically, studies need to be performed in the at-risk population with multiple, validated tests at clinically prescribed doses in acute and chronic situations. Individual outliers must be noted during analysis for safety events rather than means or medians of populations. Studies need to take into account the effect of dosing regimens,

Main Points

- Central nervous system (CNS) effects have been documented in various patient populations and to varying degrees in case reports, brain activity surrogates, and computerized cognitive testing, but not in phase III or community studies.
- Comorbid conditions common in older patients, or additional medications with anticholinergic activity may make older patients more susceptible to cognitive impairment and exaggerate the antimuscarinic drug effects on cognitive function.
- Molecular size, charge, and lipophilicity of parent and any active metabolites need to be considered for blood–brain barrier penetration and CNS pharmacological effects.
- Transdermal delivery of oxybutynin provides a more stable serum level and favorably alters the levels of the parent compound oxybutynin to the metabolite N-desethyloxybutynin and may influence oxybutynin penetration and its effects on the CNS.

with doses selected to represent commonly prescribed doses with equivalent bladder potency. The alterations in the serum levels and parent/metabolite effects contributed by metabolic issues or drug delivery systems require special attention. Metabolic issues such as alterations in cytochrome P450 metabolism or drug–drug interactions may define critical subpopulations.

Anticholinergic CNS effects have been documented in various patient populations and to varying degrees in case reports, brain activity surrogates, and computerized cognitive testing, but nowhere as profoundly as in phase III or community studies. At this time, no individual method has been determined to be definitive. Elderly patients, and in particular the cognitively impaired, are thought to be at greater risk with contributions from the aging BBB, polypharmacy effecting drug–drug interaction and, in particular, anticholinergic load, and a decreasing metabolic reserve acknowledged as additional risk factors. The CNS effects of anticholinergic-AM agents are a serious and complex issue about which we cannot afford to be confused. ■

Dr. Staskin is a consultant to Watson Pharmaceuticals, Inc.

References

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327-336.
2. Andersson KE, Yoshida M. Antimuscarinics and the overactive detrusor: which is the main mechanism of action? *Eur Urol*. 2003;43:1-5.
3. Andersson KE. Bladder activation: afferent mechanisms. *Urology*. 2002;59(Suppl 5A):43-50.
4. Volpicelli LA, Levey AI. Muscarinic acetylcholine receptor subtypes in cerebral cortex and hippocampus. *Prog Brain Res*. 2004;145:59-66.
5. Hegde SS, Eglen RM. Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. *Life Sci*. 1999;64:419-428.
6. Ruggieri MR Sr, Braverman AS. Regulation of bladder muscarinic receptor subtypes by experimental pathologies. *Auton Autacoid Pharmacol*. 2006;26:311-325.
7. Singh BN. Increased heart rate as a risk factor for cardiovascular disease. *Eur Heart J*. 2003;(5 Suppl G):G3-G9.
8. Messer WS Jr, Bohnett M, Stibbe J. Evidence for a preferential involvement of M1 muscarinic receptors in representational memory. *Neurosci Lett*. 1990;116:184-189.
9. Anagnostaras SG, Murphy GG, Hamilton SE, et al. Selective cognitive dysfunction in acetylcholine M1 muscarinic receptor mutant mice. *Nat Neurosci*. 2003;6:51-58.
10. Van de Waterbeemd H, Camenisch G, Folkers G, et al. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. *J Drug Target*. 1998;6:151-155.
11. Pak RW, Petrou SP, Staskin D. Trospium chloride: a quaternary amine with unique pharmacological properties. *Curr Urol Rep*. 2003;4:436-440.
12. Guay DR, New K. Poster presented at the 37th annual meeting of the American Society of Health-System Pharmacists. Atlanta, GA: December 8-12, 2002.
13. Appell RA, Chancellor MB, Zobrist RH, et al. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. *Mayo Clin Proc*. 2003;78:696-702.
14. Pakulski C, Drobnik L, Millo B. Age and sex as factors modifying the function of the blood-cerebrospinal fluid barrier. *Med Sci Monit*. 2000;6:314-318.
15. Starr JM, Wardlaw J, Ferguson K, et al. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *J Neurol Neurosurg Psychiatry*. 2003;74:70-76.
16. Abdel-Rahman A, Abou-Donia SM, El-Masry EM, et al. Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum. *J Toxicol Environ Health A*. 2004;67:163-192.
17. Aizenberg D, Sigler M, Weizman A, et al. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients. *Int Psychogeriatr*. 2002;14:307-310.
18. Doraiswamy PM, Leon J, Cummings JL, et al. Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2002;57A:M173-M177.
19. Katz IR, Sands LP, Bilker W, et al. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc*. 1998;46:8-13.
20. Banerjee S, Routledge PA, Pugh S, et al. Poisoning with oxybutynin. *Hum Exp Toxicol*. 1991;10:225-226.
21. Choulot JJ, Mensire A, Saint Martin J. Overdose of anticholinergic agents and confusional syndrome [in French]. *Ann Pediatr (Paris)*. 1989;36:714.
22. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. *J Am Geriatr Soc*. 2002;50:1165-1166.
23. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc*. 2003;78:687-695.
24. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc*. 2001;76:358-363.
25. Chapple C, Steers W, Norton P, et al. A pooled analysis of 3 phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int*. 2005;95:993-1001.
26. Staskin D, Sand P, Zinner N, et al. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol*. 2007;178(3 Pt 1):978-983.
27. Wagg A, Wyndaele JJ, Sieber P. Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. *Am J Geriatr Pharmacother*. 2006;4:14-24.
28. Valsecia ME, Malgor LA, Espindola JH, et al. New adverse effect of oxybutynin: "night terror" [letter]. *Ann Pharmacother*. 1998;32:506.
29. Diefenbach K, Donath F, Maurer A, et al. Randomized, double blind study of the effects of oxybutynin, tolterodine, trospium chloride and placebo on sleep in healthy young volunteers. *Clin Drug Invest*. 2003;23:395-404.
30. Diefenbach K, Arold G, Wollny A, et al. Effects on sleep of anticholinergics used for overactive bladder treatment in healthy volunteers aged > or = 50 years. *BJU Int*. 2005;95:346-349.
31. Brickenkamp R, Zillner E. The d2 Test of Attention (d2). In: Testkatalog 2000/2001. Testzentrale, Göttingen. Bern: Hogrefe-Verlag; 2000:60.
32. Pietzko A, Dimpfel W, Schwantes U, Topfmeier P. Influences of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. *Clin Pharmacol*. 1994;47:337-343.
33. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol*. 2001;41:636-644.
34. Kay GG, Wesnes KA. Pharmacodynamic effects of darifenacin, a muscarinic M selective receptor antagonist for the treatment of overactive bladder, in healthy volunteers. *BJU Int*. 2005;96:1055-1062.
35. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol*. 2006;50:317-326.
36. Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. *J Urol*. 2005;173:493-498.
37. Chapple C, Dubeau C, Ebinger U, et al. Darifenacin treatment of patients ≥ 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. *Curr Med Res Opin*. 2007;23:2347-2358.
38. Perry EK, Kilford L, Lees AJ, et al. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol*. 2003;54:235-238.